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apparatus and techniques

Evaluation of nebulizers for use in neonatal ventilator circuits

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The use of nebulizers in neonatal ventilator circuits offers a new and relatively uncharted route of therapy for infants in respiratory failure. We used a model lung to investigate and compare different nebulizer types and therapeutic agents and to make practical observations.

Five different nebulizers (Ultravent, Acorn, MAD2, Small Particle Aerosol Generator, and Pulmosonic) were compared for efficiency of delivery of an aminophylline aerosol to the model lung, and the particle size of aerosol produced by them was measured. A Nebulizer Efficiency Index (NEI) was created, representing the deposition rate of the original solution as aerosol upon the model lung filter. The Acorn ($2.8 \cdot 10^{-3}$ ml/min) and MAD2 ($2.4 \cdot 10^{-3}$) scored highest NEI.

When a suspension of budesonide was nebulized, minimal amounts of drug were recovered from the filter when the nebulizer producing the smallest particle size (Ultravent) was studied, suggesting that suspensions of drugs behave differently from solutions.

Significant changes need to be made to a conventional circuit when jet nebulizers are used; most of these are obviated by the use of an ultrasonic nebulizer, which also avoids the potential problem of marked cooling of the gas flow produced by jet nebulizers. (Crit Care Med 1990; 18:866)

There is increasing interest in inhalation therapy for respiratory conditions in ventilated neonates and infants. This route offers considerable advantages, in particular, the ability to deliver high local concentrations of drug to the respiratory system, while avoiding high systemic concentrations with associated undesirable side-effects (1).

However, in a ventilator circuit, considerable amounts of aerosol tend to be expelled with waste gas, or to be deposited on ventilator tubing, connectors, endotracheal (ET) tubes, and proximal airways without reaching the distal airways (2). Delivery to the peripheral lung may be improved by reducing aerosol particle size (3). Studies so far have focused on volume-cycled ventilation which is not widely used in neonatal and infant practice, and which entails a significantly different mode of operation to constant flow devices (4). The introduction of nebulizers into ventilator circuits can also bring hazards, particularly relating to deposition of crystalline material in pressure relief valves (4).

The use of a suspension rather than a solution for nebulization may have implications for the efficiency of the nebulizer-ventilator circuit; this particular aspect has not been examined previously. If the particle size of the suspension employed is larger than the aerosol mass median diameter produced by the nebulizer, significant amounts of drug may simply remain in the nebulizer while the suspension medium itself forms the bulk of the aerosol produced.

This study compared the abilities of five representative nebulizers to deliver an aerosol solution to a model lung using a pressure-limited, time-cycled ventilator circuit. Results were combined with particle size data to determine a Nebulizer Efficiency Index (NEI). We also examined the efficiency of three of our test nebulizers to deliver nebulized budeosonide suspension. The relative practical merits of the different nebulizers in the ventilator circuit were also considered, paying particular attention to ease of operation.

MATERIALS AND METHODS

The five nebulizers studied included four jet nebulizers: Ultravent (Mallinkrodt, Maryland Heights, St. Louis, MO); Acorn (Medic Aid, Chichester, UK); MAD2 (Astra Meditec, Lund, Sweden); Small Particle Aerosol Generator (SPAG) (Viratek, Costa Mesa, CA); and one ultrasonic nebulizer: Pulmosonic (Devilbiss, Somerset, Philadelphia, PA). These models represent five nebulizer types potentially available for use in a ventilator circuit. The Ultravent jet nebulizer produces a very small particle size and is widely used for lung imaging. The Acorn is a standard jet nebulizer extensively used for bronchodilator therapy. The MAD2, a new jet nebulizer, combines both high output and small

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particle size (5) and has been designed specifically for use in a ventilator circuit. The SPAG, a larger model, is currently used for the administration of the antiviral agent ribavirin in infants with bronchiolitis; it has been recommended for use in both volume-cycled and pressure-limited ventilation (4). The Pulmosonic is an ultrasonic nebulizer also used for bronchodilator therapy. Three units of each nebulizer were used in this study, apart from the MAD2, where only one unit was available.

Nebulizers were inserted into a ventilator circuit (Fig. 1). No humidifier was present in the circuit as the nebulizers themselves achieved humidification. The ventilator was a Neovent 90 (Vickers Medical, Basingstoke, UK), a pressure-limited, time-cycled device. Smooth-walled reusable ventilator tubing was used, with right-angled ET tube connector and shouldered 3.5-mm ET tube (Portex, Hythe, UK). Aerosol was collected in a filter (Aerosol Medical, Colchester, UK) impinger system inserted at the tip of the ET tube just proximal to the rubber test lung (Drager, Hemel Hempstead, UK).

Aminophylline (25 mg/ml) was used as the nebulized substance, because an accurate assay was available. Nebulizers were each loaded with 4-ml aminophylline solution, except for the SPAG, which required a 100-ml fill of aminophylline solution. After ventilation, aminophylline was eluted from the filters with 10 ml of sterile water, and levels were measured using high-performance liquid chromatography (Applied Chromatography Systems, Luton, Beds, UK). The filter collection system was validated by double elution of a single filter, and by comparing aerosol deposition in two filters attached in series at the end of the ET tube.

Ventilation was performed for 5 min in each experiment at 20/2 cm H_2O, inspiratory/expiratory ratio of 1:1, and respiratory rate of 30 breath/min. This provided a 15-ml tidal volume (VT) to the rubber test lung and a minute ventilation of 450 ml. Gas flow for the circuit was provided entirely through the nebulizer for the Ultravent (8 L/min), Acorn (8 L/min), MAD2 (6 L/min, maximum flow possible), and SPAG (8 L/min). The SPAG was also used at the recommended flow rates of 6 L/min, both with and without the one-way valve (4) and, at this setting, an additional gas flow of 2 L/min was provided to the ventilator circuit in the conventional manner. The drying chamber gas flow was adjusted to zero in the SPAG, as recommended (4). With the Pulmosonic nebulizer, gas flow at 8 L/min was provided in the conventional manner since the nebulizer produces aerosol by ultrasonic piezoelectric crystal oscillation, rather than by gas jet flow.

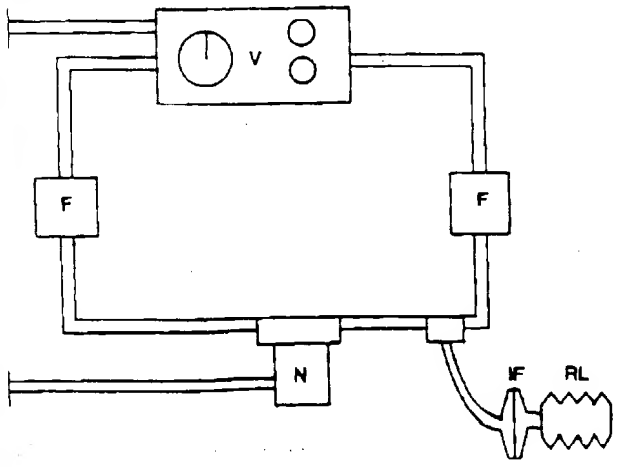

FIG. 1. Circuit diagram. *N*, nebulizer; *V*, ventilator; *F*, filters on inspiratory and expiratory limbs; *IF*, impinging filter; *RL*, rubber model lung. Aerosol deposited on the impinging filter was eluted and measured.

Each nebulizer was connected at the circuit to a T-piece 24 cm from the ET tube connector. Nebulizers were weighed before and after each period of use to determine output, without correction for evaporation. In the case of the SPAG, which is a sizable piece of equipment, the reservoir flask alone was weighed. Each individual nebulizer was studied on three occasions, except for the SPAG models and the single MAD2, which were studied on five occasions each.

Nebulizing a Suspension

An identical experimental circuit was used, except that budesonide suspension (500 μg/ml) was used in place of aminophylline and that only the Acorn, Ultravent, and MAD2 nebulizers were studied. Filters were eluted with ethanol; analysis of deposited budesonide was performed (Draco Laboratories, Lund, Sweden). Each nebulizer type was examined on five occasions.

Aerosol Size

Aerosol mass median diameter (AMMD) was measured using a laser particle sizer (2600, Malvern Instruments, Malvern, UK). Aminophylline (25 mg/ml) was used as the test substance. Nebulizers were drivencat flow rates identical to those described above. AMMD was measured both at the nebulizer exit port and at the tracheal end of an ET tube after the aerosol had passed through a T-piece, ventilator tubing, and connector to represent the particles presented to the model lung. During measurements, the aerosol was released 2 cm from the laser beam. AMMD for each individual nebulizer was studied on three occasions, except for the MAD2 ($n = 5$) and the SPAG nebulizers ($n = 10$).

RESULTS

Nebulizing a Solution

A second elution of the filter yielded 10.7% of the first elution ($n = 5$). A second filter, connected in series

with the first, trapped a further 6% of the drug deposited (n = 3). Accordingly, the filter system was considered an efficient one for the purposes of comparison of aerosol presented to the respiratory tract at the end of the ET tube.

The amount of aminophylline deposited in each filter varied enormously between nebulizers (Table 1). When the data for nebulizer output and filter deposition were combined, the MAD2 achieved the greatest deposition of aerosol as a percentage of output.

Nebulizing a Suspension

Minimal amounts of budesonide were retrieved from filters when the Ultravent was used; the MAD2 had the highest delivery to the filter overall (Table 2).

Aerosol Size

The AMMD was consistently lower for the Ultravent at the two different sample sites than for the other nebulizers (Table 3). With the exception of the SPAG, the AMMD was smaller at the ETT than at the nebulizer exit port. The percentage of aerosol contained in particles <4 μ at the ET tube was not predictable from a knowledge of the nebulizer outputs.

Nebulizer Efficiency Index

Combination of results of filter deposition, nebulizer output, and particle sizing allowed the estimation of an NEI for ventilator circuits; the Acorn and MAD2 scored highest in terms of the rate at which they delivered aerosol particles of <4 μ to the filter (Table 4).

DISCUSSION

The results underline the problems of aerosol delivery in neonatal ventilator circuits; the great majority of particles are either carried away in the continuous flow of the circuit or are deposited on ventilator tubing and connectors. However, it is clear that appropriately sized particles can be delivered during ventilation.

Aerosol delivery in mechanically ventilated adult patients is significantly lower than in spontaneously breathing adults (6). Animal models simulating infant volume preset, time-cycled ventilation have been used. Thus, a nebulizer producing submicronic particles gave greater deposition rates than other standard jet nebulizers (7), while a small particle size was observed to increase peripheral rather than central deposition (3). In a rubber bag model, alteration of frequency and V_T, but with a constant minute ventilation, produced no change in aerosol deposition rate (8).

Most neonatal units employ pressure-limited, time-cycled ventilation with a continuous-flow circuit. This circuit necessitates different strategies for introduction of a nebulizer from those employed with volume-cycled ventilation. Unless synchronized nebulization is used (3), considerable amounts of aerosol are lost in the continuous flow. Therefore, it is apparent that aerosol delivery during pressure-limited ventilation will be less efficient than in volume-preset, time-cycled ventilation.

Aerosol particle size also seems to be of great significance in determining delivery of aerosol (7). Particles deposit in three main fashions: impaction (particles >5 μ), sedimentation (particles from 1 to 5 μ), and diffusion (submicronic) (9). Each of these mechanisms tends to operate in a different lung region such that impaction tends to occur at the carina and other junctions, sedimentation in smaller airways where the flow is decreased, and diffusion in alveoli. A proportion of submicronic aerosol will behave as a gas and will be exhaled without coming into contact with the respiratory lining (9). Increased flow rate will increase the tendency of smaller particles to impact (9). Excess mucus in airways will also tend to trap aerosol presented to the airways (10). All of these factors should be considered when

TABLE 1. Nebulization of a solution (aminophylline)

	No. of Observations	Aminophylline per Filter (mg/5 min, mean ± SD)	Output (ml/min) (%)	Proportion of Aerosol Deposited on Filter (%)
Ultravent	9	0.054 ± 0.015	0.18	0.22
Acorn	9	0.38 ± 0.09	0.34	0.88
MAD2	5	0.37 ± 0.11	0.19	1.52
SPAG[a]	15	0.026 ± 0.015	0.14	0.15
Pulmosonic	9	0.22 ± 0.20	0.28	0.60

[a] At 6 L/min with one-way valve in situ.

TABLE 2. Nebulization of a suspension (budesonide)

	No. of Observations	Budesonide per Filter (μg/5 min, mean ± SD)	Output (ml/min) (%)	Proportion of Aerosol Output Deposited on Filter (%)
Ultravent	5	0.2 ± 0.01	0.14	0.06
Acorn	5	9.0 ± 0.2	0.37	1.08
MAD2	5	17 ± 0.2	0.25	2.72

TABLE 3. Aerosol mass median diameter (μ)

	No. of Observations	At Nebulizer	At ETT	Proportion of Aerosol <4 μ (%)
Ultravent	9	1.8	1.2	94
Acorn	9	4.5	1.3	93
MAD2	5	2.1	1.9	82
SPAG*	10	6.8	9.5	60
Pulmosonic	9	6.4	2.9	66

* At 6 L/min with one-way valve in situ.

TABLE 4. Nebulizer efficiency index (ml/min)*

Ultravent	0.0004
Acorn	0.0028
MAD2	0.0024
SPAG[b]	0.0001
Pulmosonic	0.0011

* Rate of delivery of solution, as particles <4 μ, to the model lung.
[b] At 6 L/min with one-way valve in situ.

attempting to assess aerosol delivery in ventilated infants.

Deposition of aerosol in the infant lung may differ from deposition on our filter both in terms of total volume and regional deposition. The use of radioaerosol would provide a good measure of aerosol dose delivered, and of distribution, but ethical considerations preclude the use of radioisotopes in infants. An alternative strategy might be to nebulize a substance which can be measured subsequently in urine or blood and which is harmless or even potentially beneficial to infants. However, the variable ventilator requirements and difference in lung pathology from infant to infant would seriously restrict attempts to compare different nebulizers. Accordingly, we feel that our filter model, although in some respects an inadequate representation of human lungs, offers a useful model for nebulizer comparison.

One potential problem encountered in this route of therapy is malfunction of pressure relief valves due to precipitation of solute crystals, leading to pneumothorax. Gas may flow backward through the inspiratory limb when jet nebulizers are used, and therefore, not only expiratory (4), but also inspiratory limb filters, may need to be used. One-way valves in inspiratory limbs have been suggested (11) but these would cause dangerously high pressures during inspiration.

A further potential problem is the low temperature of aerosol presented to the infant. Previous experience suggested a decrease of up to 20°C airway temperature can be expected during a 10-min nebulization period with a jet nebulizer that may in itself have significant effects on airway function. However, ultrasonic nebulizers do not cause this cooling effect. Use of a heated wire within the inspiratory limb may prevent this problem but will alter particle size by evaporation.

When nebulizers are used in ventilator circuits as the main source of driving gas, small but significant adjustments may be required in the pressure settings. Of the nebulizers studied, only the SPAG would add significantly to the deadspace of ventilation; this might lead to blunting of the "square wave" of pressure, leading to reduced V_T especially at high rates. None of the other nebulizers would affect the pattern of ventilation.

The raining out of aerosol phenomenon may lead to fluid trickling down the ET tube with consequent presentation of the drug as a liquid rather than aerosol. This may be minimized by the use of a nebulizer with a low AMMD and by maintaining an appropriate gradient on the inspiratory line between nebulizer and infant. Under these circumstances, the amount of fluid loading with nebulizers should not materially affect lung function or fluid balance, being a maximum of 2.7% of the nebulizer output, in our studies (Tables 1 and 2).

The Acorn achieved the highest NEI. It is cheap, widely available, and simple to use. The change in AMMD from nebulizer orifice to ET tube tip is reflected in a moderate degree of raining out of the aerosol in the ventilator tubing. The Acorn had the highest output of the nebulizers studied, which allows for rapid aerosol administration.

The MAD2 also achieved a high NEI. It is not yet commercially available but may prove extremely useful. This prototype has the advantage of being reusable; however, we found it to be particularly prone to clogging if left without cleaning, presumably due to the small size of the gas and fluid orifices.

The Ultravent produces a relatively monodisperse aerosol with a low AMMD. Although it had a low NEI, the small particle size will theoretically allow good penetration of particles to the lung peripheries. It is convenient to use, but currently only available with the radioaerosol kit.

The SPAG 2 is already used widely for ribavirin administration in children with acute viral bronchiolitis. It can be used in ventilator circuits "where special expertise is available" (12). It is cumbersome and complicated to set up. There was considerable variation in particle size between the three models studied, in contrast to published reports (4). Moderate amounts of raining out occurred, and the SPAG 2 achieved the lowest NEI of the various nebulizers studied. As yet, its use is limited to ribavirin administration, and the poor showing in our study may well have some bearing on the controversy currently surrounding ribavirin efficacy (13). However, it has the unique advantage of being able to nebulize large quantities of drug over long periods.

Ultrasonic nebulizers have several advantages. No gas flow is required to produce the aerosol. This means that it can be inserted into a ventilator circuit without adjustment of the ventilator settings, and without the

problems associated with retrograde gas flow in the inspiratory limb. It is reusable, readily available, and does not produce airway cooling. However, the output is variable (14) and the particle size tends to be relatively large and heterodisperse. This results in a low NEI and copious raining out. Ultrasonic nebulizers working at higher frequencies are being introduced; they may offer a more appropriate particle size (15).

The nebulization of a suspension resulted in a marked difference in efficiency between the MAD2 and the Ultravent. The latter barely delivered any budesonide to the filter. Presumably, this is because the particle size of budesonide in the suspension was considerably larger than the AMMD produced by the Ultravent; accordingly, only a small fraction of the drug could be aerosolized. This finding is of considerable significance in the choice of nebulizers for delivering suspensions. To maximize the output, the nebulizer AMMD should approximate to, or be greater than the mass median diameter of the particles in suspension.

Although nebulizers in our model all have a relatively low efficiency of aerosol delivery to the filter, it is nevertheless apparent that it is possible to use the inhaled route of therapy in the neonatal setting. Several authors (16, 17) reported the efficacy of bronchodilators in infants ventilated for bronchopulmonary dysplasia; and work is currently in progress on the use of nebulized disodium cromoglycate solution and topical steroid suspensions in newborn infants. Careful selection of appropriate nebulizers and attention to the specific circuit adjustments required could see the emergence of the inhaled route of therapy in ventilated neonates as a major advance.

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REFERENCES

1. Brain JD, Valberg PA: Deposition of aerosol in the respiratory tract. *Am Rev Respir Dis* 1979; 120:1325
2. Ahrens RC, Ries RA, Popendorf W, et al: The delivery of therapeutic aerosols through endotracheal tubes. *Pediatr Pulmonol* 1986; 2:19
3. Dahlback M, Karlberg IB, Nebrink O, et al: Deposition of tracer aerosols in the rabbit respiratory tract. *J Aerosol Sci* 1987; 18:733
4. Demers RR, Parker J, Frankel L, et al: Administration of ribavirin to neonatal and pediatric patients during mechanical ventilation. *Respir Care* 1986; 31:1188
5. Dahlback M, Nerbrink O, Arborelius M, et al: Output characteristics from three medical nebulisers. *J Aerosol Sci* 1986; 17:563
6. MacIntyre NR: Aerosol delivery in intubated, mechanically ventilated patients. *Crit Care Med* 1985; 13:81
7. Flavin M, MacDonald M, Dolovich M, et al: Aerosol delivery to the rabbit lung with an infant ventilator. *Pediatr Pulmonol* 1986; 2:35
8. Fraser I, DuVall A, Dolovich M, et al: Therapeutic aerosol delivery in ventilator systems. *Am Rev Respir Dis* 1981; 123:107
9. Clarke SW, Pavia D: Aerosols and the Lung. Woburn, MA, Butterworths, 1984
10. Kim CS, Eldridge MA: Aerosol deposition in the airway model with excessive mucus secretions. *J Appl Physiol* 1985; 59:1766
11. Outwater KM, Meissner HC, Peterson MB: Ribavirin administration to infants receiving mechanical ventilation. *Am J Dis Child* 1988; 142:512
12. Policy statement: Ribavirin therapy of respiratory syncytial virus. *Pediatrics* 1987; 79:475
13. Isaacs D, Moxon ER, Harvey D, et al: Ribavirin in respiratory syncytial virus infection. *Arch Dis Child* 1988; 63:986
14. Newman SP, Pellow PGD, Clarke DW: In vitro comparison of Devilbiss jet and ultrasonic nebulizers. *Chest* 1987; 92:991
15. Pillay M, Akkermans JA, Cox PH: A high efficiency ultrasound nebuliser for radioaerosol studies of the lung. *Eur J Nucl Med* 1987; 13:331
16. Gomez-Del Rio M, Serhardt T, Hehre D, et al: Effect of a beta-agonist nebulization on lung function in neonates with increased pulmonary resistance. *Pediatr Pulmonol* 1986; 2:287
17. Motoyama EK, Fort MD, Klesh KW, et al: Early onset of airway reactivity in premature infants with bronchopulmonary dysplasia. *Am Rev Respir Dis* 1987; 136:50

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